REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 104-108, 121, 123, 127-135, and 142 are now pending in this application, following the present amendments

Claims 136-141, 143, 144 and 155 have been canceled from the application.

Claims 104-108, 123, 127, 128, 131, 133-135 and 142 have been amended to more particularly point out and distinctly claim the invention.

The amendments to claim 104 are supported at page 7 lines 11-22. The amendments to claim 105 are supported at page 7, lines 11-22. The amendments to claim 106 are supported at page 7, lines 11-22. The amendments to claim 107 are supported at page 7, lines 11-22. The amendments to claim 108 are supported in the portions of the application referred to above with respect to the above amendments and at page 7, lines 23-25 and 30-32. The amendments to claim 123 are believed to be formal in nature as are the amendments to claim 127 making it independent. The amendments to claim 128 are also believed to be formal in nature and claims 121, 129, 130, 132 and 133 are merely reiterated. The amendments to claims 131 and 135 are formal in nature as are the amendments to claims 134 and 142. No new matter has been added.

Response in General

Although applicants traverse the rejections as applied, the amendments to the claims are believed to place the claims in a form which is clearly allowable in view of the rejections put forth within the Office Action. Specifically, the scope of claim 104 is more precisely defined to indicate that the claimed antibody binds to all of human, mouse and rat connective tissue growth factors. Accordingly, the claim is not merely a claim to an antibody which would bind to any of these connective growth factors. The connective growth factor obtained from each animal has a different amino acid sequence and different epitopes. Accordingly, an antibody which binds to all of the connective growth factors from any of the recited animals is specifically defined. Further, applicants have deposited hybridomas which produce specific antibodies encompassed by the invention making it possible for those skilled in the art to produce antibodies encompassed by the claims. Applicants have specifically disclosed and described how to make and use the claimed antibodies and as such have met the written description requirement. With respect to the prior art rejections applicants point out that applicants specifically claim monoclonal antibodies

whereas the prior art is teaching polyclonal antibodies and not monoclonal antibodies as claimed. The secondary references teach nothing more than general methodology and do not contain any specific teachings with respect to producing monoclonal antibodies which would bind to all of human, rat and mouse connective tissue growth factors.

Accordingly, the 35 U.S.C. §112 and 35 U.S.C. §102/103 rejections are believed to have been overcome. Should the Examiner require further details with respect to precisely how the present claims overcome the specific rejections the Examiner is referred to the sections provided below.

With respect to 35 U.S.C. §112, second paragraph rejections the Examiner has objected to specific language. Applicants have eliminated this language from the claims thereby rendering the rejections moot.

Rejections under 35 USC 112, First Paragraph

Enablement:

Claims 104-108, 121, 123, 127-135, 142, and 155 were rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to enable one in the art to make and use the invention (enablement rejection).

A "Statement of Availability" is attached hereto acknowledging the deposit criteria noted by the Examiner. Also, applicants have attached a copy of a catalog that shows details of the cell line available from ATCC -. This copy serves as clear and convincing evidence that the 293-T cell line is "readily available to the public" as required by 37 CFR 1.802(b). The catalog details are available from the ATCC web site below.

http://phage.atcc.org/cgi-bin/searchengine/longview.cgi?view=ce,691450,CRL-1573&text=CRL-1573

With regards to the other enablement issues, the rejection argues that the specification does not reasonably provide enablement for a laundry list of embodiments by stating the following reasons:

The specification does not provide any guidance as how to make and use ***any*** antibody that binds to ***any*** mammalian CTGF polypeptides other than the specific CTGF, a full length rat CTGF and human CTGF (see, lines 10-13 on page 5).

It is unpredictable which undisclosed antibody would bind to just ***any*** mammalian CTGFs and would have the same functional characteristics as monoclonal antibody produced by hybridoma BP-6208

and hybridoma BP-6209 (see, lines 21-24 on page 5).

It follows that ***any*** cell or hybridoma producing ***any*** undisclosed non-human monoclonal antibody is not enabled.

It also follows that ***any*** labeled undisclosed non-human monoclonal antibody or portion thereof and kit comprising ***any*** undisclosed non-human monoclonal antibody are not enabled.

Thus, the rejection argues, that the specification as filed, fails to enable one skill in the art to practice the invention without undue experimentation.

Claim 104 is amended to show that it does not intend to cover *all* the non-human antibodies that bind to ***any one of*** mammalian CTGFs. The antibody claimed has to bind to *all three CTGFs*, namely human, rat and mouse CTGFs. To avoid any confusion, Applicants have amended independent genus claim 104 not only to narrow the claim scope, but also to more clearly define the antibody by a structural limitation, i.e. the isotype of the antibody (see Appendix A). Therefore, the claimed antibody now has to bind to all of human, rat and mouse CTGFs, and also has to be an IgG.

As Fig.1 of the present application shows, many embodiments within this genus other than 8-64-6 (FERM BP-6209), 8-86-2 (FERM BP-6208), namely 8-97-3, 8-149-3, 15-38-1, 17-132, 24-53, 24-67, and 2-228-1, have been demonstrated. Thus, applicants have disclosed a representative number of species in the claimed genes as required by law.

Claims 105, 106 and 107 are dependent on claim 104, but have been further restricted by entering other functional, structural and/or mammalian species limitations.

Thus, the Applicants believe that all the enablement rejections have now been overcome.

Written Description:

Claims 104, 106, 108, 121, 123, 128-135, 142, and 155 were further rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter which was not described in such a way as to convey possession of the claimed invention (written description rejection).

Similar to the above enablement rejection, the examiner alleges that the specification does not provide a sufficient written description for a laundry list of embodiments stating that the specification fails to describe additional representative species of non-human monoclonal antibody that binds to just about ***any*** CTGFs (see, line 11-13 on page 7).

As mentioned above, not only the genus claim (claim 104), but also the other dependent antibody claims have now been appropriately amended to restrict the claim scope.

C. Rejections under 35 USC 112, Second Paragraph

Claims 106, 108, 131, and 135 were rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for the following reasons:

(i) the recitation of a "property substantially equivalent to" as recited in claims 106 and 108 is sufficiently indefinite and ambiguous, such that one skilled in the art would not be able to ascertain the metes and bounds of the claim; and

(ii) the recitation of a "with other substances" as recited in claims 131 and 135 is sufficiently indefinite and ambiguous, such that one skilled in the art would not be able to ascertain the metes and bounds of the claim.

As apparent from the amendment, claims 106, 108, 131, and 135 no longer have the above terminology objected to by the Examiner. Accordingly, Applicants submit that the claims as amended meet the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request reconsideration and withdrawal of the rejection.

D. Rejections under 35 USC 102

Claims 104, 106, 108, and 155 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat No. 5,408,040 issued April 1995 to Grotendorst et al. The rejection argues that the '040 patent teaches a monoclonal antibody that binds to human CTGF that would inherently cross-react with mouse and perhaps rat CTGF, given that the immunogen used to generate the reference antibody is a full length human CTF wherein the amino acid sequence has a large region identical to mouse and rat.

Claims 104, 106, 108, 121, 123, 128-132 and 155 were further rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pat No. 5,783,187 issued July 1998 to Grotendorst et al. The rejection argues that the '187 patent teaches a mouse monoclonal antibody (which is non-human) and screening hybridoma that binds to human CTGF as well as methods for using such antibodies in detecting CTGF levels and in affinity column chromatography. The rejection then argues that the claimed properties are inherent, given that the immunogen used to generate the reference antibody is a full length human CTF wherein the amino acid sequence has a large region identical to mouse and rat.

The rejections are traversed as applied and as they might be applied to the presently pending claims. The cited art does not disclose monoclonal antibodies but rather discloses polyclonal antibodies as

pointed out in detail below. In that the cited art does not disclose monoclonal antibodies which, as claimed, bind to all of human, mouse and rat connective tissue growth factors. Because the cited art does not disclose the claimed invention or teach how to make such monoclonal antibodies, the art fails to disclose "each and every element" of the claims. Therefore, the cited art does not anticipate the claimed invention..

All the above rejections were made by citing either one or both of the US Pat. 5,408040 ('040 patent) and US Pat.5,783,187 ('187 patent). The '187 patent was issued from a divisional application of US application No. 167,628 filed on Dec. 14, 1993, now '040 patent. Accordingly, all the descriptions, except issued claims of the '187 patent, are completely identical to that of the '040 patent, which has been confirmed by the Applicants. Therefore, it is sufficient to address only the '040 patent when responding to the rejections.

Reviewing the '040 patent specification, it is apparent that the subject matter of the present claims is not disclosed or suggested in the '040 patent.

The '040 patent specification describes,

> *<Lines 47-60 in column 7>*
>
> *"Purified PDGF or synthetic peptides containing the amino and carboxyl sequences of the mature PDGF A and B chain molecules were used to raise antibodies in goats.* ***Goats were immunized with 20μg of purified PDGF or 50μg of synthetic peptide*** *in Freunds complete adjuvant by multiple intradermal injections.* ***Immune sera were collected*** *seven days after the fourth rechallenge (in Freunds incomplete adjuvant) and subsequent rechallenges. The* ***anti-PDGF antibody*** *did not show any cross-reactivity to TGF-β, EGF, or FGF in immunoblot analysis. The anti-peptide antibodies were sequence specific and did not cross-react with other synthetic peptide sequences or with recombinant PDGF peptides which did not contain the specific antigenic sequence." (emphasis added)*

Thus, the inventors of the '040 patent succeeded in isolating the human CTGF as defined in Claim 1 of the '040 patent using an eventual profile of the **antisera** (in other words, a **polyclonal** antibody) collected from the goat immunized with **human PDGF** (not any mammalian CTGF).

Accordingly, the '040 inventors have neither produced a cell that produces any specific monoclonal antibody against any mammalian CTGF, nor any monoclonal antibody produced therefrom,

not to mention that they have not disclosed or suggested any monoclonal antibody of the present application. Therefore, since the '040 patent fails to disclose or suggest the monoclonal antibody of the present invention, none of the cells, the monoclonal antibody-immobilized carrier, or a labeled monoclonal antibody, are disclosed or suggested therein.

The '040 patent fails to teach any of the claimed inventions, and furthermore, the claims as amended herein define the antibody both in terms of structural and functional characteristics that are not mentioned in the '040 patent. Therefore, the instant inventions cannot be anticipated from the '040 patent and the Applicants respectfully request reconsideration and withdrawal of the rejections.

Rejections under 35 USC 103

Claims 121 and 123 were rejected under 35 U.S.C. § 103(a) for being unpatentable over Grotendorst '040 in view of Harlow et al. (*Antibodies: A Laboratory Manual*, 1988).

The rejection is traversed as applied and as it might be applied to the presently pending claims. In essence, the '040 patent does not disclose monoclonal antibodies and the Harlow et al. article does nothing more than provide general teachings with respect to making monoclonal antibodies. The combination of the two references does not teach towards applicants' invention which is a specific monoclonal antibody having specific characteristics and not taught in the prior art.

Grotendors's '040 patent does not teach cells producing the antibody, more particularly hybridomas obtained by fusing a mammalian myeloma cell with a mammalian B cell producing the antibody of interest. Harlow et al. is cited for the premise that the making of such cells is known in the art. Thus, the rejection argues that one of ordinary skill in the art would have been motivated to create the claimed cells and would have had a reasonable expectation of success in producing the claimed invention.

Furthermore, claims 131-135 and 142 were rejected under 35 U.S.C. § 103(a) for being unpatentable over Grotendorst '040 or '187 in view of U.S. Pat. No. 6,107,049 issued to Mucke et al.

According to the rejection, the Grotendorst patents do not disclose the specific labeled antibodies, labeling agents, and kits utilizing immobilized carriers as claimed. Mucke et al. is cited for the premise that detection kits and reagents are well known and routinely used in the art. Thus, the rejection concludes that one of ordinary skill in the art would have been motivated to create the claimed labeled antibodies and kits and would have had a reasonable expectation of success in producing the claimed invention.

This rejection is also traversed as applied and as it might be applied to the presently pending claims. The rationale for the traversal is described above and further described below.

As mentioned above, the '040 patent discloses only a polyclonal antibody and not the monoclonal antibody of the instant invention that binds to all human, rat and mouse CTGFs. The Hallow reference merely relates to general methodology for preparing a hybridoma which produces a monoclonal antibody. Since the '040 patent does not disclose the monoclonal antibody of the instant invention, the instant invention cannot be obvious from the '040 patent or Harlow et al, either alone or in combination.

Similarly, one cannot "substitute the polyclonal CTGF antibody as taught by the '040 patent" (OA, page 12, line 7) for "the kit as taught by the '049 patent", because the '040 patent" does not disclose the same monoclonal antibody of the instant invention. Therefore, the instant invention is not be obvious from the '040 patent or '049 patent, either alone or in combination.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number SHIM006.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 30/May/02

By: _____
Karl Bozicevic
Registration No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\SHIM (Shimizu, formerly SHI)\006\amend to oa 1-28-02.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please cancel claims 136-141, 143, 144 and 155 from the application without prejudice to the filing of the claims to this subject matter in the future.

Please amend the claims as shown below.

104. (Twice Amended) A non-human monoclonal antibody or a portion thereof, which **(a) binds** [is reactive] to **all of** human, mouse and rat connective tissue growth factors (CTGFs) **and (b) has the IgG isotype**.

105. (Twice Amended) The non-human monoclonal antibody or a portion thereof according to claim 104, wherein said [monoclonal] antibody **inhibits the binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL 1573)** [is produced by a hybridoma identified by international deposit accession No. FERM BP-6208].

106. (Twice Amended) The non-human monoclonal antibody or a portion thereof according to claim 104, wherein said [monoclonal] antibody **is a mouse, rat or hamster antibody** [comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by international deposit accession No. FERM BP-6208].

107. (Twice Amended) The non-human monoclonal antibody or a portion thereof according to claim **106** [104], wherein said [monoclonal] antibody **inhibits the binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL 1573)** [is produced by a hybridoma identified by international deposit accession No. FERM BP-6209].

108. (Twice Amended) **A** [The] non-human monoclonal antibody or a portion thereof**, which is** [according to claim 104, wherein said monoclonal antibody comprises a property substantially equivalent to that of a monoclonal antibody] produced by a hybridoma identified by international deposit accession **numbers selected from the group consisting of FERM BP-6208 and** [No.] FERM BP-6209.

121. (Reiterated) A cell producing the non-human monoclonal antibody according to claim 104.

123. (Twice Amended) The cell according to claim 121, wherein said cell is a hybridoma **obtained** [obtainable] by fusing a mammalian myeloma cell with a mammalian B cell **that produces** [which is capable of producing] the non-human monoclonal antibody.

127. (Twice Amended) **A** [The] cell [according to claim 121, wherein said cell is a hybridoma] identified by international deposit accession numbers selected from the group consisting of FERM BP-6208 and FERM BP-6209.

128. (Twice Amended) An antibody-immobilized insoluble carrier **comprising** [on which] the non-human monoclonal antibody according to claim 104 **or claim 108** [is immobilized].

129. (Reiterated) The non-human antibody-immobilized insoluble carrier according to claim 128, wherein said insoluble carrier is selected from the group consisting of plates, test tubes, tubes, beads, balls, filters and membranes.

130. (Reiterated) The non-human antibody-immobilized insoluble carrier according to claim 128, wherein said insoluble is a filter or membrane, or that used for affinity column chromatography.

131. (Twice Amended) A labeled antibody **comprising** [which is prepared by labeling] the non-human monoclonal antibody or a portion thereof according to claim 104 **or claim 108 that is labeled** with a labeling agent **that provides** [capable of providing] a detectable signal [by itself or together with other substances].

132. (Reiterated) The labeled non-human monoclonal antibody according to claim 131, wherein said labeling agent is an enzyme, fluorescent substance, chemiluminescent substance, biotin, avidin, or radioisotope.

133. (Amended) A kit for detecting or assaying mammalian CTGF, comprising the non-human monoclonal antibody or a portion thereof according to claim 104 **or claim 108**.

134. (Twice Amended) A kit for detecting or assaying mammalian CTGF comprising an antibody-immobilized insoluble carrier **which comprises** [on which] the non-human monoclonal antibody according to claim 104 **or claim 108** [is immobilized].

135. (Twice Amended) A kit for detecting or assaying mammalian CTGF comprising a labeled antibody **which comprises** [which is prepared by labeling] the non-human monoclonal antibody or a portion thereof according to claim 104 **or claim 108 that is labeled** with a labeling agent **that provides** [capable of providing] a detectable signal [by itself or together with other substances].

Please cancel claims 136-141.

142. (Twice Amended) A kit for separating or purifying mammalian CTGF, comprising an antibody-immobilized insoluble carrier **which comprises** [on which] the non-human monoclonal antibody according to claim 104 **or claim 108** [is immobilized].

Please cancel claims 143 and 144.

Please cancel claim 155.